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KURT PETTERSSON

Stereochemical studies in the α-aryl carboxylic acid series with special reference to phenyl- and 2-thienyl-substituted compounds

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Stereochemical Studies in the α-Aryl Carboxylic Acid Series with Special Reference to Phenyl and 2-Thienyl Substituted Compounds

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BY

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Stereochemical studies in the α-aryl[1] carboxylic acid series with special reference to phenyl- and 2-thienyl-substituted compounds

By Kurt Pettersson

With 10 figures in the text

Chemical reactions between asymmetric compounds occur frequently in the field of biochemistry. A study of these reactions should therefore give valuable information about biological processes and an increasing understanding of such important problems as metabolism and drug action. But even from a purely chemical viewpoint these reactions are of considerable interest, not only because they afford an increasing knowledge of this interesting class of compounds, but also because they constitute valuable aids for the study of more general problems as, for example, reaction mechanisms.

An important question concerning asymmetric compounds is their configurational relation which may be determined by chemical and physical methods. Although the problem of absolute configuration has been solved in principle by Bijvoet (11), it is generally more convenient to determine the configuration of a compound relative to that of a given standard substance, usually D-glyceraldehyde. Since the absolute configuration of this substance is known from the work of Bijvoet, it follows that the absolute configuration of compounds related to this standard is also known.

Correlation of compounds containing a phenyl group directly linked to an asymmetric carbon atom and aliphatic compounds often presents some difficulties (12, 13, 14), and at the beginning of the present work only a few α-phenyl carboxylic acids had been related to D-glyceraldehyde (15). A method for establishing the mutual relation within the group has been proposed by Kuhn (16). The method is based upon the assumption that the phenyl group has a dominating influence on the optical activity of the compounds, and therefore those compounds which have the same mode of rotation have also the same configuration.

Analogously constituted phenyl and thienyl compounds often show far-reaching similarities in their physical and chemical behaviour. It seemed to be of interest, therefore, to compare the properties of analogously constituted compounds containing phenyl and 2-thienyl groups directly attached to an asymmetric center. Since phenyl and thienyl compounds are often isomorphic, it seemed highly probable that the steric relations could be determined by means of the quasi-racemate method. A comparison of the influence of the aromatic groups on the optical activity of the compounds and their ability to form racemates should also throw some light on these interesting phenomena.

[1] Carbocyclic as well as heterocyclic groups with aromatic properties are here considered as aryl groups.

Material and methods of preparation

The compounds studied may be classified in three different groups: The α,β-diarylpropionic acids (arylmethyl-arylacetic acids), the arylsuccinic acids and the α-phenyl fatty acids (alkylphenylacetic acids). The formulae of the compounds are collected in Fig. 1.

The members of the first group consist of the four acids obtained if the two aryl groups possess the four possible combinations of phenyl and 2-thienyl (I, II, III, IV) (17). In general, these acids may be obtained by alkylation of the corresponding arylacetonitriles (18) or ethyl arylmalonates (19, 20), followed by hydrolysis to the acids and decarboxylation of the malonic acids. However, it is often more convenient to alkylate the esters of the arylcyanoacetic acids, since these reactions often give higher yields and more pure products. For that purpose ethyl 2-thienylcyanoacetate was prepared by carbethoxylation of 2-thienylacetonitril (1, 94), and the alkylation of the ester as a method for preparation of α-(2-thienyl)-substituted acids was demonstrated (1, 2, 17).

The optical resolution of the diarylpropionic acids were successful except in the case of the dithienylpropionic acid (III) (of which only one of the antipodes could be obtained) (4, 5). There are usually three criteria of optical purity: The constancy of the optical activity upon further recrystallisations of the alkaloid salt, a sharp melting point of the compound and agreement between the optical activities of the antipodes obtained with different alkaloids. If, however, the antipodes form a continuous series of mixed crystals, as in the case of the dithienylpropionic acid, a small melting-point interval is no indication of optical purity. Since the rotation of the (−)-acid was considerably higher than that of the (+)-acid, the third criterion fails also. It is probable, however, that the (−)-α,β-di(2-thienyl)propionic acid obtained is at least not very far from optical purity (*vide infra*).

2-Thienylsuccinic acid (XII) was prepared mainly according to three general methods: (i) Carbethoxymethylation of ethyl 2-thienylcyanoacetate, followed by decarboxylation and hydrolysis of the resulting ethyl α-(2-thienyl)-α-cyanosuccinate (2); (ii) addition of potassium cyanide to ethyl 2-thenalmalonate, alkaline hydrolysis of the resulting ethyl β-(2-thienyl)-β-cyanopropionate to the corresponding acid and subsequent hydrolysis of the cyanoacid in boiling water (3); (iii) addition of potassium cyanide to ethyl α-cyano-β-(2-thienyl)acrylate, followed by acid hydrolysis of the resulting ethyl α,β-dicyano-β-(2-thienyl)propionate in a mixture of ether and hydrochloric acid (3).

The physical properties of the optically active 2-thienylsuccinic acids indicate that the resolution is complete. The antipodes as well as the optically inactive acid decompose at the melting points, probably forming anhydrids. In addition, the antipodes racemize under various conditions (3).

The five lowest members of the α-phenyl fatty acid series from hydratropic acid to α-phenyloenanthic acid were resolved into optical antipodes and used as intermediates in the correlation of the diarylpropionic acids to D-glyceraldehyde (Fig. 1, formulae V through IX) (8, 10). As far as the author knows, the three higher members of the series have not been fully resolved earlier. The resolutions were performed with the enantiomorphs of α-phenylethylamine. It is interesting to note that hydratropic acid differs from the four other acids in so far as the (+)-acid is obtained with the *dextro*-rotatory amine, whereas of the other acids the (−)-acid is obtained. The optically active acids, except those of hydratropic acid, could not be crystallized.

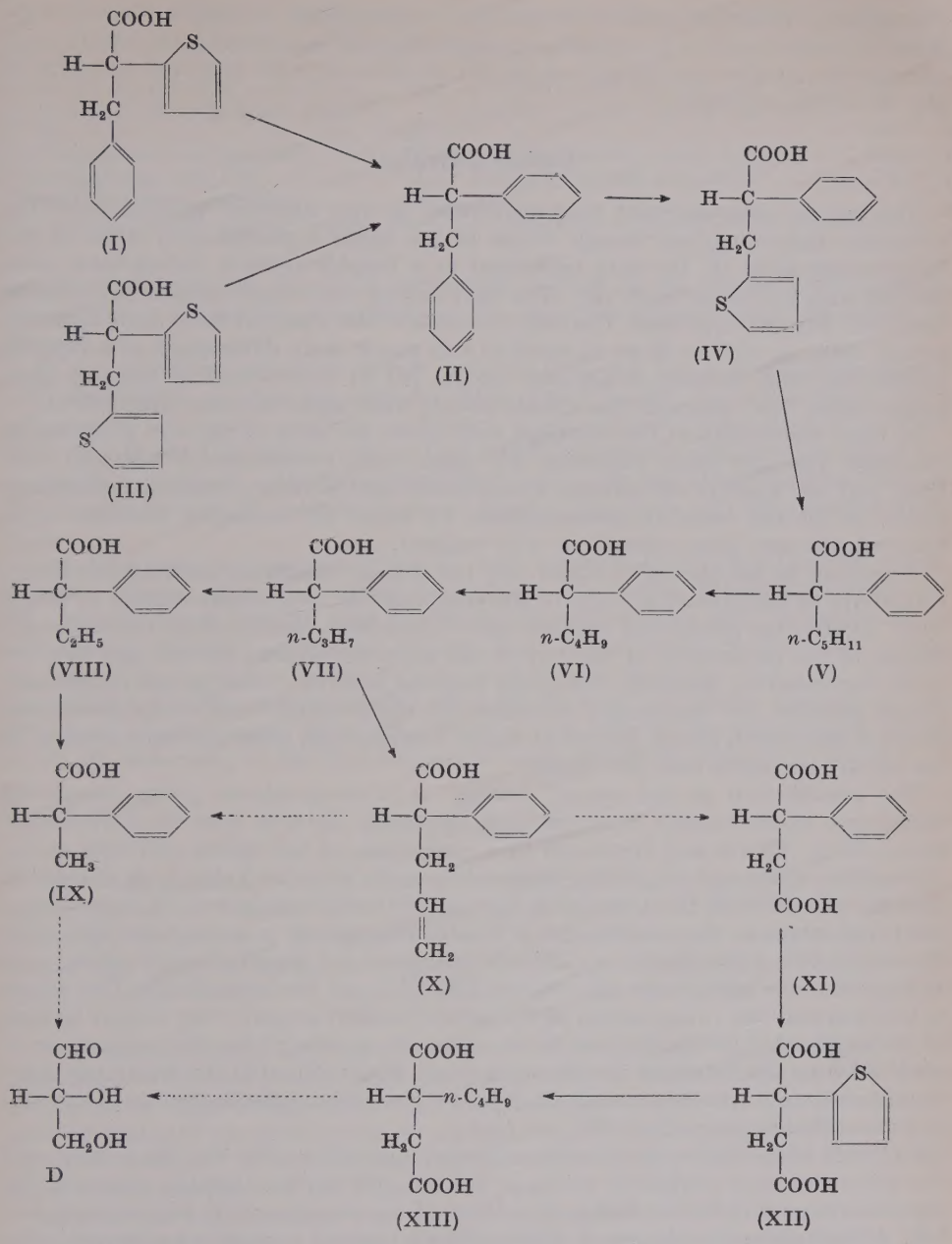


Fig. 1. Sterically related acids. All of the compounds are *dextro*-rotatory. Relations not determined by the author are indicated by dotted arrows.

Attempts to initiate crystallisation with the corresponding crystalline racemic acids were without success. It is probable, therefore, that these racemates are true racemic compounds. Amides and anilides of several of the acids were prepared and used in the steric investigations.

Optical activities

The optical measurements were performed in two different polarimeters. The definitive determinations except those of the liquid α-phenyl fatty acids in the homogenous state (8, 10) were performed in a Lippich-Landolt half-shadow polarimeter with petroleum bath (21). The light source was a conventional 6 V electric bulb with bayonet-type base. The measurements of the α-phenyl fatty acids in homogenous state, as well as those reported in this paper, were determined in a Lippich polarimeter from Schmidt & Haensch (model 14174) with a sodium lamp as light source. With this apparatus the measurements were made at room temperature.

In each determination five readings were made for each of the two positions of the tube. The zero point correction was made from measurements with the tube filled with the appropriate solvent. The solvents used were of commercial analytical grade. In the less accurate measurements, by which the resolution processes were followed, the zero point corrections were omitted.

According to the theory of Kuhn (22) the groups around an asymmetric center contribute to the optical activity of the compound in two fundamentally different ways. Firstly, the group may contain active absorption bands, which under the influence of the asymmetry of the rest of the molecule (vicinal action) give rise to a direct contribution. Secondly, the group together with two other groups around the center provides the asymmetry necessary for the polarization of active absorption bands in the fourth group. The most active bands in this sense are those located in the ultraviolet region near the visible.

The contribution to the optical activity of a chromophoric group containing anisotropic bands, rapidly decreases with increasing distance from the asymmetric carbon atom. This is well illustrated by a comparison of the optical activities of the arylsuccinic acids and the arylmethylsuccinic acids given in Table 1. It is evident that the contribution from the phenyl group of benzylsuccinic acid is decreased to the same extent as the contribution from the alkyl group in *n*-pentylsuccinic acid. The similarities between the arylsuccinic acids and the diarylpropionic acids, containing the same aryl groups (II, XI and III, XII), are also remarkable. This seems to indicate that the vicinal action of the carboxymethyl group is very similar to that of the arylmethyl group. It must be remembered, however, that the comparison is made between the activities in only one solvent. If the values in the remaining three common solvents are compared (5, 6), it is easily seen that only the values of the ions in water differ by more than 10 %.

In Table 1 the acids with an α-phenyl group are collected in the left column and the acids with an α-(2-thienyl) group in the right. It is clear that the values in the right column are definitely lower than those of the corresponding derivative in the left. According to the theory of Kuhn (16) the optical activity of α-phenylacetic acids in the visible region is predominantly determined by the phenyl band located at about 2500 A. It is tempting to assume that the 2-thienylacetic acids behave in a similar manner and that the optical activity of these compounds is mainly determined by the thienyl absorption band, probably located at about 2300 A (26). Whether the

Table 1. $[M]_D^{25}$ of α-aryl carboxylic acids in ethanol.

α,β-diphenylpropionic acid (II) (5)	277°	α,β-dithienylpropionic acid (III) (5)	196°
α-phenyl-β-thienylpropionic acid (IV) (4)	265°	α-thienyl-β-phenylpropionic acid (I) (4)	181°
phenylsuccinic acid (XI) (6)	280°	2-thienylsuccinic acid (XII) (6)	206°
benzylsuccinic acid (23)	43.5°	2-thenylsuccinic acid (24)	16.5°
n-pentylsuccinic acid (25)	49.4°		

lower activities of the thiophene compounds depend on the shorter wave-length of absorption or on smaller anisotropy of the absorption band cannot be settled at present.

In the preceding paragraph it was assumed that the (−)-α,β-dithienylpropionic acid obtained is at least not very far from optical purity. An indication of this is afforded by the optical activities in Table 1. A comparison of the values of the three first acids in the two columns shows that dithienylpropionic acid occupies about the same place between α-thienyl-β-phenylpropionic acid and thienylsuccinic acid as diphenylpropionic acid between α-phenyl-β-thienylpropionic acid and phenylsuccinic acid.

Since the thienyl compounds evidently have lower optical rotation than the corresponding phenyl compounds one could perhaps expect that dithienylpropionic acid should have lower rotation than α-thienyl-β-phenylpropionic acid. However, the β-aryl groups probably act mainly through their vicinal action on the α-aryl group, and the vicinal action is caused by a state of coupled electrons. It is quite probable that such a coupling is more readily obtained between two similar aromatic groups with their similar energy states than between two different aromatic groups. If this is so, the behaviour of the diarylpropionic acids should be as shown in Table 1.

Steric relations

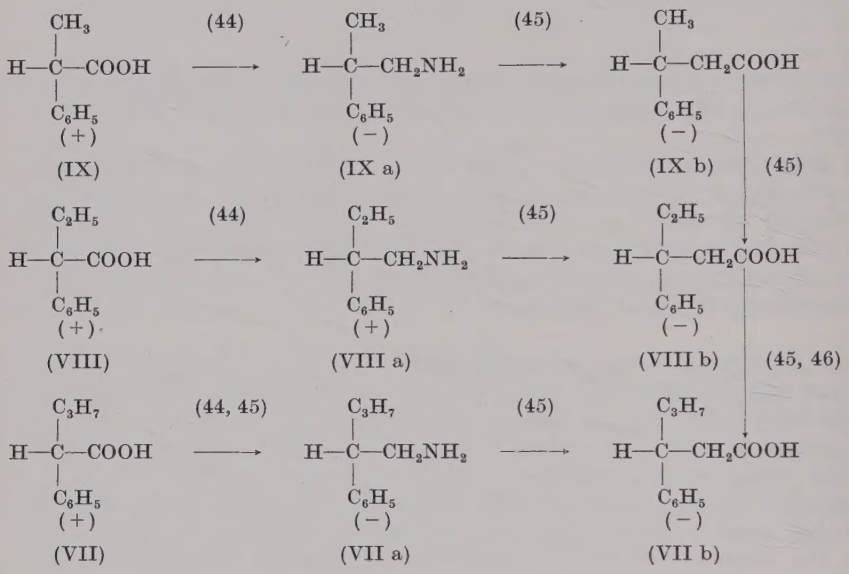
The configurational relation between the acids investigated is shown in Figure 1, where the steric formulae according to the convention of Emil Fischer (27) are collected. The sequence of substances ends in two points with compounds (hydratropic acid (IX) and *n*-butylsuccinic acid (XIII)), previously related to glyceraldehyde by other authors. It seems justified, therefore, to shortly summarize these works.

In a thermal study of alkylsuccinic acids and alkylsulfidesuccinic acids Matell found that the *n*-alkylsuccinic acids with the same mode of rotation have also the same configuration (28). Fredga (29) related methylsuccinic acid and mercaptosuccinic acid by means of the quasi-racemate method and in a similar way mercaptosuccinic acid and malic acid (30). The latter acid was related to glyceraldehyde through the intermediate tartaric acid (31, 32).

Hydratropic acid has been converted to α-phenethylamine by several rearrangement reactions, known to proceed with retention of configuration (33, 34, 35). Oxidative degradation of the phenyl group in the amine yields alanine (12), related to lactic acid (36, 37, 38). Mislow related hydratropic acid and lactic acid through mandelic acid (39, 14). Lactic acid is related to glyceraldehyde through isoserine (40, 41). Fredga related hydratropic acid and allylphenylacetic acid (X) (42) which

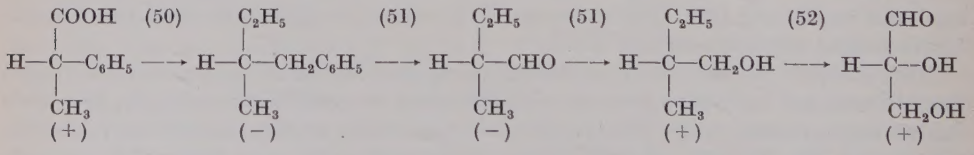
was oxidized to phenylsuccinic acid (43). The last-named acid is related to glyceraldehyde as shown in Figure 1.

Levene *et al.* have published, in a series of papers (44–48), a steric investigation including among other substances hydratropic acid (IX) and its two next homologues (VIII, VII). For the purpose of convenience the main relations are shown in the scheme below (compare 48). Frequently occurring formal errors in the papers as well as repeated



corrections of the signs of rotation (46, 47) leave the reader somewhat uncertain as to the correctness of the results. It seemed to be of interest, therefore, to test the very surprising relation between the amines in the second column (VII a–IX a). The amides of the optically active phenyl fatty acids (VII–IX) were hydrogenated to the corresponding amines by means of lithium aluminium hydride (see experimental part). The sign of rotation of the amines was found to be in accordance to those obtained by Levene *et al.* It seems to the author that a study of the rotatory dispersion of these amines as well as their homologues would be of interest, since alternating rotatory powers in homologous series of this kind are rather unexpected.

Evidence for the D-configuration of the *dextro*-rotatory hydratropic acid may be found in the enormous steric work by Levene *et al.*, if their "rules of masses" are correct (which is evidently not the case for the amines discussed above) (compare 49):



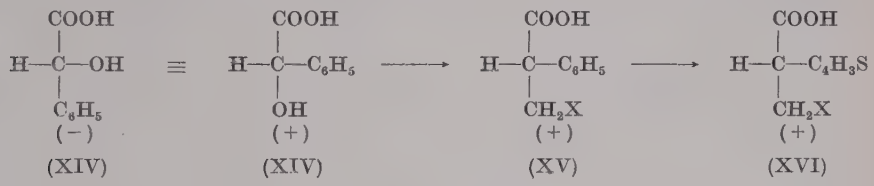
The steric relation between the diarylpropionic acids (I), (II) and (IV) was established by means of the quasi-racemate method and by comparison of the optical

activities in different solvents (4, 5, 7. *Vide infra*). The conclusion about the configuration of α,β-di(2-thienyl)propionic acid (III) is based only on the results of the optical method (5).

Reductive desulfurization of the thienyl group in optically active α-phenyl-β-(2-thienyl)propionic acid (IV) yields active α-phenyloenanthic acid (V) (9) and correlation between the configurations of the compounds of the diarylpropionic acid series and those of the α-phenyl fatty acid series was thus obtained. The members of the last-mentioned series were connected amongst themselves by the quasi-racemate method applied to the amides and by the optical displacement rule (9, 10. *Vide infra*). Allylphenylacetic acid (X) was connected to α-phenyl-*n*-valeric acid (VII) by catalytic hydrogenation of the allyl double bond (9).

The arylsuccinic acids (XI, XII) were correlated by means of the quasi-racemate formed between the acids with opposite mode of rotation (6). Reductive desulfurization of the aromatic group in optically active 2-thienylsuccinic acid yielded *n*-butylsuccinic acid (XIII) with the same direction of rotation (3).

All acids except (XIII) were related by comparison of their optical activities in different solvents. It is interesting to note that the method, proposed by Kuhn (16) and briefly mentioned in the introduction, is applicable not only to the substituted phenylacetic acids investigated but also to the analogous 2-thienylacetic acids. (The succinic acids may, of course, be considered as substituted acetic acids). It should be pointed out that the relations, shown in the formulae XIV, XV and XVI, give a possible but less common correlation between mandelic acid and glyceraldehyde.



Stereochemical methods

Chemical methods

As is well known, a reaction which does not involve the rupture of a bond to an asymmetric carbon atom in general proceeds with retention of the configuration. This is always the case if only one of the groups around the center is attacked. The reactions referred to in this paper are of this type.

As was pointed out in the introduction a correlation of aromatic and aliphatic compounds by chemical means is often difficult to perform (12, 13, 14). Physical methods such as the quasi-racemate method or optical methods are probably not applicable because of the great structural differences between such compounds. Therefore, the convenient method described by Fredga in 1953 was very opportune (25). According to this method the thiophene nucleus is desulfurized with Raney nickel, forming the corresponding aliphatic compound. Since phenyl and thienyl compounds often give quasi-racemates (6, 7, 24, 53) the method is very useful for the correlation of phenyl compounds to glyceraldehyde. In this way α-phenyl-β-(2-thienyl)propionic acid (IV) was converted to α-phenyloenanthic acid (V) (9) and 2-thienylsuccinic acid (XII) to *n*-butylsuccinic acid (XIII) (3).

It is perhaps somewhat superfluous to mention that the desulfurization process is by no means limited to thiophene compounds. However, a more special application of the method may be emphasized. As will be discussed more thoroughly in the following paragraph the possibilities for two compounds to form quasi-racemates depend on the structural similarity between them. Fredga has shown that the differences may be reduced, if a common large substituent is introduced into both substances (36, 54, 55, 56). Sulfur-containing groups are often easily introduced (as for example a phenylmercapto group) and also easily removed by means of Raney nickel.

Catalytic reduction of the allyl double bond in allylphenylacetic acid (X) yielded the corresponding α-phenylvaleric acid (VII) (9).

The quasi-racemate method

1. RACEMATE FORMATION.—The optically inactive substance, obtained from equimolar quantities of two optical antipodes may, if solid, be classified in one of three different groups, depending on its crystal behaviour (57). Most commonly a molecular compound, i.e. a racemate, is formed, which has physical properties different from those of the enantiomers and may be detected by different physical methods. A melting-point diagram of such a system shows, in general, the molecular compound as a maximum, surrounded by two symmetrically situated eutectic points. More rarely, the inactive substance is a solid solution of the antipodes (a pseudo-racemate), and crystallizes in the same crystal form as these. The melting-point diagram shows in this case the inactive solution as a maximum or minimum point in the middle of the diagram, which in some rare cases may contain other maximum or minimum points (58). It is also possible that the inactive solution may appear as the middle point of a straight line connecting the melting points of the antipodes (59). Finally, the inactive substance may constitute a eutectic mixture, i.e. a conglomerate, of the antipodes, and appears in the melting-point diagram as a eutectic point (60). It may also be mentioned that the antipodes as well as the antipode plus the racemate (10, Figs. 1 and 2) may show more or less far-reaching solid solubility. This fact seems to be but little discussed in the literature and is scarcely noticed in the usual textbooks.

Little is known about the factors which cause the inactive substance to crystallize in a certain form, for example as a racemic compound. Probably these factors are also responsible for the stability of the racemates, and this stability in turn seems to be of great importance for the question of quasi-racemate formation (*vide infra*). Landrieu (61) advanced the view that compounds such as acids and salts which are able to form ions should also tend to form true racemates, whereas undissociable compounds should form pseudo-racemates. Ross and Somerville (62) found that strongly associating substances give racemic compounds and feebly or not associating substances give pseudo-racemates or conglomerates. On the other hand Matell (60) found that β-oxy-β-phenylpivalic acid gives a conglomerate, whereas its methyl ester gives a true racemate.

The stability of a racemic compound is indicated by the energy change in the reaction

$$l\text{-A} + d\text{-A} = rac.\text{-A}$$

which may be determined calorimetrically. However, more convenient methods are desired and, therefore, the height of the maximum in the melting-point curve, the

extent of the middle branch of the curve or the difference between the melting point of the racemate and the transition point, beyond which the racemate is unstable, have frequently been used as indications of the stability of the racemate. Findlay and Campbell (63) found that the stability of racemic acid (optically inactive dihydroxysuccinic acid) is about the same as that of its methyl ester, whereas acylation of the hydroxyl group of the ester considerably decreased the stability of the racemate. On the other hand, acylation and esterification of mandelic acid caused respectively a slight and a considerable increase in this stability (64).

Since the results summarized above are in part contradictory and inconsistent it seems to the author to be of value to note every relation between structure and racemate-formation tendency that might be found. A collection of experimental facts could perhaps complete the picture of this particular type of molecular compound, the formation of which is still little understood. In fact, the present material seems to be well suited for this purpose, since it consists in part of a homologous series (9, 10), making it possible to follow the influence of a continuous change in one of the groups around the asymmetric center, and in part of compounds in which a phenyl group has been replaced by a 2-thienyl group (4, 5, 6). Since these groups are known to have similar properties in many respects, it is of interest to find out if an interchange of the groups in different compounds is reflected in the racemate-formation tendency.

The homologous series consists of the amides of the five lowest members of the α-phenyl fatty acid series (V–IX). Unfortunately, the behaviour of the corresponding acids is not known with certainty, since, as mentioned above, only the antipodes of hydratropic acid are obtained in the crystalline state. It is rather probable, however, that the crystalline inactive acids (all except α-phenylcaproic acid) are true racemates, since attempts to seed the antipodes with the corresponding racemate were without success[1]. If the crystalline inactive acids were pseudo-racemates or conglomerates, they should contain crystals with the same crystal form as the antipodes, and should then be well suited as seedlings for the latter. Therefore, it seems justified to suppose that the inactive acids are true racemates with, as it seems, considerably higher melting points than the antipodes. If this is so, the stability of the racemates is lowered by conversion to the amides (9, 10).

As already mentioned, the racemate-formation tendency may be indicated by the distance between the eutectics or the difference in melting point between the racemate and the eutectic, and also by the difference between the racemates and the antipodes (63). Usually these measurements give indications in the same direction, for example, a great racemate-formation tendency corresponds to a large distance between the eutectics, a large difference between the melting points of the racemate and the eutectics, and a large positive difference between the melting points of the racemates and the antipodes. A small racemate-formation tendency corresponds to a small distance between the eutectics, a small difference between the melting points of the racemate and the eutectics and so on. In the case of hydratropamide the relations are somewhat uncertain (10). The inactive amide is a true racemate, melting only about 1.5° higher than the eutectics, indicating a low ability of racemate formation. The middle branch of the curve occupies about half of the diagram, indicating a moderate tendency for racemate formation and the difference of −7° between the racemate and the antipodes indicate a comparatively low tendency. It seems to the

[1] The results of Pickard and Yates (91) concerning α-phenylvaleric acid could not be reproduced (8).

author that if a comparison between several compounds is performed, it should be better to consider the height of the maximum *in comparison to* the difference between the melting points of the antipodes and the eutectics. A ratio less than 0.5 could then be classified as a small racemate-formation tendency, a ratio between 0.5 and 1.5 as moderate and a ratio greater than 1.5 as strong. These values usually correspond to a distance between the eutectics of less than 50 %, 50–75 % and more than 75 % of the diagram, respectively. Of course, this classification is quite arbitrary, but it might give a substantiation of the expressions small, moderate and great racemate-formation tendency used in the text.

The stability of the racemates of the homologous alkylphenylacetamides (9, 10) varies in an irregular manner. The lowest stability is shown by the racemic α-phenylvaleramide, which is a little less stable than hydratropamide. The racemate-formation tendency of these compounds must be classified as small. More stable are the racemic α-phenylbutyramide with a moderate and the racemic α-phenylcaproic and α-phenyloenanthic amides with a great tendency for racemate formation. It is obvious that substances belonging to a homologous series may show considerable differences in the racemate-formation tendency (compare also 56). Since the association tendency of the amides in question is of at least the same order of magnitude and probably varies in a regular manner, the results indicate that factors other than the association ability are also involved in the racemate formation.

If the diarylpropionic acids (I, II, III, IV) are considered (4, 5), one finds that the racemate-formation tendency decreases in the order α,β-diphenylpropionic acid (great) > α-thienyl-β-phenylpropionic acid (moderate) > α-phenyl-β-thienylpropionic acid (small) > α,β-dithienylpropionic acid, which does not form a true racemate at all. The exchange of a phenyl group for a 2-thienyl group evidently affects the ability for racemate formation to an extent which *cannot be explained by the difference in the association tendency*. Furthermore, the association of the dithienyl compound should be greater than for the diphenyl compound because of the expected greater acidity, and the results are then contradictory to the theory of Ross and Somerville (62).

If two optically active acids are isomorphic, one could perhaps expect that they should also have similar capacities to combine with their antipodes to form racemic compounds. It is well known that analogously constituted compounds, containing phenyl and thienyl groups, are often isomorphic. If the tendency of forming racemates is only or predominantly a crystallographic property, one could then expect that the racemate-formation tendency should be of the same order for the thienyl and phenyl compounds. Among the substances under discussion the arylsuccinic acids are isomorphic (6), but unfortunately this case is complicated by polymorphism. It is remarkable, however, that the more stable modification of the optically inactive phenylsuccinic acid is a true racemate, whereas the single known modification of the inactive 2-thienylsuccinic acid is very likely a pseudo-racemate.

An inspection of the behaviour of the diarylpropionic acids from this point of view affords some interesting observations. The acids may be paired in three different groups in respect to the groups around the asymmetric center: (1) those which have the same aryl group in the α-position but different groups in the β-position; (2) those which have different aryl groups in the α-position but the same group in the β-position; and (3) those with different aryl groups in both the α- and β-positions. In the first group we have the two pairs α,β-diphenylpropionic acid (II)–α-phenyl-β-thienylpropionic acid (IV) and α-thienyl-β-phenylpropionic acid (I)–α,β-dithienylpropionic

acid (III); in the second group the two pairs α,β-diphenylpropionic acid (II)–α-thienyl-β-phenylpropionic acid (I) and α-phenyl-β-thienylpropionic acid (IV)–α,β-dithienylpropionic acid (III); and in the third group the pairs α,β-diphenylpropionic acid (II)–α,β-dithienylpropionic acid (III) and α-phenyl-β-thienylpropionic acid (IV)–α-thienyl-β-phenylpropionic acid (I). Since an aryl group in the α-position has fewer degrees of freedom in respect to the asymmetric center than in the β-position, one should expect that the paired substances in the first group should show more similar properties than those of the other groups. This is indeed the case. The first pair of the first group is isomorphic (7, Fig. 3), whereas the second pair with some probability is isodimorphic (7, Fig. 5). In the other groups some pairs show far-reaching solid solubility, but in no case is there any indication of crystallographic similarity (4, 5, 7). If, now, the racemate-formation tendency is in some way related to the crystallographic behaviour, the paired substances of the first group should resemble each other in their ability to form racemates, i.e. α-phenyl-β-thienylpropionic acid (IV) should have greater ability for racemate formation than α-thienyl-β-phenylpropionic acid (I). But from Figs. 1 and 2 in (4) it is evident that the facts are quite the contrary and again no relation between isomorphism and racemate-formation tendency could be found. The differences between α,β-dithienylpropionic acid and α-thienyl-β-phenylpropionic acid are noteworthy since their antipodes are probably isodimorphic, whereas the optically inactive forms are so clearly different, the first being a pseudo-racemate and the second a true racemate with moderate stability.

Hitherto the only compounds considered are those with isomorphic enantiomers. Still more reliable results would be obtained if the racemic compounds were also isomorphic. This is not the case for the arylsuccinic acids which could be investigated with X-rays (6). Neither has a complete investigation of isomorphism between the racemic diarylpropionic acids been performed, but a thermal investigation of contact preparations showed that only α,β-diphenylpropionic acid (II) and α-thienyl-β-phenylpropionic acid (I) could possibly be isomorphic. However, benzylsuccinic acid and the two isomeric thenylsuccinic acids fulfil these requirements (24, 53). The tendency for racemate formation decreases in the order 2-thenylsuccinic acid (great) > benzylsuccinic acid (moderate) > 3-thenylsuccinic acid (small). Thus, the order between the phenyl and 2-thienyl compounds is reversed in comparison to the compounds discussed above, but even here the exchange of the phenyl group for a thienyl group appreciably affects the stability of the racemates.

From what has been said it is evident that the formation of racemates is a complicated phenomenon, at least not predominantly depending on either the association tendency or the crystallographic properties. It is assumed that it must be possible to bring the molecules of the two antipodes in a true racemic compound into coincidence by means of a symmetry operation (65). It has also been pointed out that the condition for two antipodes to form solid solutions is that the structure of the antipodes must not differ too much from a structure which is identical with its mirror image (65). Both these conditions depend on the structural framework of the molecule. Therefore, the differences between the phenyl- and 2-thienyl-substituted compounds are interesting, since these groups are similar chemically and have similar space requirements. It is possible that the forces arising from the sulfur atom may have an influence which may be difficult to predict. In the substituted succinic acid series a cyclized substituent seems to have a dominating influence, since the racemate-formation tendency decreases from excellent for cyclohexylsuccinic acid (58) to zero for 2-thienylsuccinic acid. On the other hand the tendency of the alkylsuccinic

acids from methyl to hexyl is of the same order, the racemates of the acids with an even number of carbon atoms in the alkyl chain being a little more stable than the others (28). It is possible, that the length of the alkyl groups is also responsible for the irregular variation of the stability of the alkylphenylacetamides. In fact, a minimum is obviously present for the *n*-propyl derivative in the alkylsuccinic acid series also (28).

2. QUASI-RACEMATE FORMATION.—The only difference between the components of a racemate is the configuration. One might ask what happens, if structural differences are also introduced. Already in 1899 Centnerszwer made the interesting observation that equimolar quantities of (+)-chlorosuccinic acid and (−)-bromosuccinic acid give a molecular compound (66). Since these acids are known to have opposite configurations (compare 56) the molecular compound must be considered as a kind of racemic compound, a quasi-racemate (67). The existence of such compounds was discussed by Delépine (68), but although this author clearly pointed out that the components have opposite configurations, the formation of these compounds as an indication of steric relation was first introduced by Timmermans (69), and in the hands of this author (70) and, above all, of Fredga *et al.* (56, 71) the method has been developed to a valuable aid in steric investigations. It is remarkable that this method, which cannot be theoretically derived, as yet has not in any case given contradictory results but has often been applicable where other methods have failed.

A quasi-racemic compound is to be considered as a true racemic compound, in which one of the components is replaced by a similarly constituted compound with the same configuration. It is evident, then, that the factors which determine the formation of the racemate also determine the formation of the quasi-racemate, but in addition, the differences between the replacing compounds must be accounted for. The first-mentioned factors may be summarized as the tendency for racemate formation. The importance of this tendency for the formation of quasi-racemates has been pointed out by Fredga (56), who found that a compound with sufficient ability for racemate formation was able to form molecular compounds with quasi-racemic character even with structurally related symmetric compounds (67). The requirements that must be demanded of a compound replacing one of the components in a racemate were discussed by Lettré (72), who proposed that the interchanging compounds should be isomorphic. However, Fredga (56) emphasized that this was too rigidly formulated, since quasi-racemates were also obtained with compounds which were not isomorphic. Nevertheless, it is a self-evident condition that the structural differences must be limited, if the basic principle for the quasi-racemate is maintained, i.e. the analogy to the true racemate (*vide infra*).

In a stereochemical study on plant growth substances Matell (73) found that the formation of quasi-racemates seems to be "more dependent on structural differences than on the racemate-formation tendency". This conclusion was drawn from a consideration of the occurrence of quasi-racemates as a function of the racemate-formation tendency. Unfortunately, the fact that the formation of a quasi-racemate is dependent on two racemate-formation tendencies was not accounted for. This difficulty is minimized, if the substances to be compared are combined with a properly chosen third substance. An example may illustrate the idea.

α,β-Diphenylpropionic acid (II), α-(2-thienyl)-β-phenylpropionic acid (I) and α,β-di(2-thienyl)propionic acid (III) have great, moderate and no racemate-formation tendency, respectively (4, 5). The structural differences between the two first-men-

tioned acids are probably greater than between the two last-mentioned, since in the first case the antipodes with the same configuration form a diagram with far-reaching solid solubility, whereas in the second case the antipodes are probably isodimorphic (7, Figs. 1 and 5). Now, the first-mentioned acids form a quasi-racemate but the last-mentioned do not, in spite of their smaller structural differences (7, Figs. 2 and 6). In this case then, the quasi-racemate formation is probably a result of the great racemate-formation tendency of α,β-diphenylpropionic acid. However, it seems rather strange to the author that a simple *general* relation should exist between such complicated and indefinite conceptions as the ability of two optical antipodes to combine to a racemate and the structural differences between one of these antipodes and a second compound.

As was pointed out above, it is necessary that a quasi-racemate should have structural similarity to a racemate. This is often manifested in that it is isomorphic to one or both of the racemates formed of its components (53, 54, 68, 74, 75). If these racemates are not isomorphic, it seems quite possible that the enantiomers with opposite configuration may adjust themselves to a molecular compound with a crystal lattice something between those of the racemates but has, nevertheless, the properties of a quasi-racemate. In such cases it may be difficult to find evidence that the compound is in fact a quasi-racemate. However, it is usually enough to show that an optically active compound gives a molecular compound with equimolar quantities of one enantiomer of another compound but not with the other. It seems to the author desirable that in such cases the structural differences between the compounds should not be too great for the following reason:

A quasi-racemate may be considered as one of two diastereomers, and the mode of detection described above is applicable only in those cases where the second diastereomer does not exist under the experimental conditions used. If the structural differences between the components are great, as for example between acids and bases, the physical properties of the diastereomers may bear no relation to the configuration of the components. This is illustrated by the failure of the rule of Winther (76). According to this rule the antipodes of different acids have the same configuration, if they are precipitated with the same alkaloid. Many cases are reported, however, where this rule fails (77, 78) and another example of this is afforded by the α-phenyl fatty acids (8, 10). It is then quite possible that the enantiomers with the same configuration form a molecular compound, but the enantiomers with opposite configuration do not (compare 54). Therefore, the fact that a molecular compound is formed with one pair of the antipodes but not with the second is not a sufficient condition for this compound to be a quasi-racemate. If, however, the structural differences between the compounds are not too great, the probability that the compound is not the quasi-racemate is rather small, but it seems to the author that in doubtful cases one should try to find crystallographic relations between the molecular compound and the racemates (compare 65).

The conception of the quasi-racemate as one of the two possible diastereomers may also explain the fact that in at least two known cases, the antipode of one compound forms molecular compounds with both antipodes of another (10, 79). The second compound is then the second diastereomer, and it remains to find a relation between one of the compounds and one or both of the racemates. The conditions may be illustrated with an example.

In a previous paper it was shown that (−)-α-phenylbutyramide gives molecular compounds with both antipodes of hydratropamide (10, Figs. 3 and 4), but no attempts

Fig. 2. Melting-point diagram for the system racemic α-phenylbutyramide and the molecular compound, consisting of equimolar parts of (+)-hydratropamide and (−)-α-phenylbutyramide.

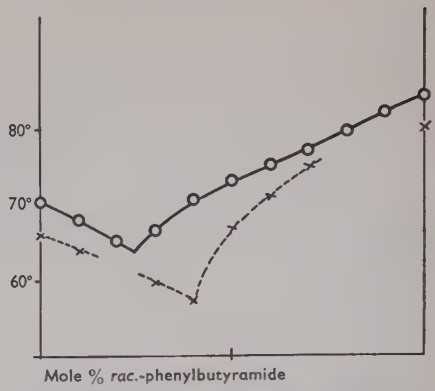


Fig. 3. Melting-point diagram for the system racemic α-phenylbutyramide and the molecular compound, consisting of equimolar parts of (+)-hydratropamide and (+)-α-phenylbutyramide.

were made to relate the compounds to the racemates. It was only assumed that the more pronounced maximum for the amides with opposite direction of rotation was an indication of the quasi-racemate. The melting-point diagram of this compound and racemic α-phenylbutyramide is given in Figure 2 of the present paper. It is evident that the compound is isomorphic to a low-melting modification of the phenylbutyramide. That this modification had not been found earlier, is explainable by the fact that it is rather unstable. The details will be discussed more thoroughly in connection with the question of polymorphism. In Figure 3 is given the diagram obtained with the molecular compound of the amides with the same mode of rotation and racemic phenylbutyramide. In this case no indication of crystallographic similarity is present. The complete melting-point diagrams of hydratropamide and the molecular compounds were not investigated, since contact preparations clearly showed no relations in these cases. The earlier assumption, that the molecular compound obtained from the amides of opposite direction of rotation is the quasi-racemate, was therefore evidently correct (10). Applied in this way the quasi-racemate method gives the same steric relation between hydratropic acid and α-phenylbutyric acid as the methods used before.

The quasi-racemate is like the racemate a molecular compound with physical properties different from those of the components. It may then be detected by different physical methods. In the investigation under discussion mainly three methods have been used: thermal analysis, X-ray diffraction, and infrared spectroscopy.

3. Thermal analysis.—The main method for establishing the presence of a quasi-racemate has been the study of melting-point diagrams (7, 9, 10). The apparatus used was a Kofler hot-stage microscope (80) with the tube protecting the thermometer removed (81). The thermometer was calibrated against azobenzene, benzil and acetanilide with the melting points 68°, 95° and 115°, respectively. The apparatus was fitted with polarizer and analyzer except when the diagrams in (7) were determined. The rate of heating was 1–2°/min.

The melting-point samples were prepared by weighing out appropriate amounts

on a torsion balance (maximal weight 10 mg, accuracy 0.02 mg) (4, 5, 7, 9) or by mixing appropriate volumes of stock solutions (10).

The compounds thermally investigated were stable under the conditions used. If not otherwise stated the compounds were considered as thermally stable, if three complete cycles of melting–crystallisation did not affect the melting point.

The melting-point examination of the samples during the melting process affords some advantages (80). The necessary amounts of the sometimes difficultly accessible enantiomeric compounds are appreciably depressed, the thaw-points are more precisely determined and polymorphic modifications are easily detected. Preliminary investigations of the systems by means of contact preparations (80) were made, but since cases are known where molecular compounds failed to crystallize in such preparations (28), the complete diagrams were also investigated.

4. X-RAY DIFFRACTION.—As is well known, simple phase analyses may be performed by means of X-ray powder photographs. The quasi-racemate as a phase different from the components also has a different powder photograph. If the quasi-racemate is isomorphous to one or both of the corresponding racemates (53) the results are easily understood, whereas in other cases the large amount of lines frequently obtained from organic lattices, may make the result difficult to interpret (6).

The X-ray diffraction method is especially of value if the substances in question are thermally unstable (6), but may also be used to verify or complement the results obtained by the thermal method (5, 10). Although polymorphic modifications may obviously be detected with this method, the occurrence of such modifications may also render the results more difficult to explain. An otherwise very unstable lattice may under certain circumstances be stabilized, as is shown in Figure 2, for example. The fact that the quasi-racemate from phenylsuccinic acid and 2-thienylsuccinic acid is not isomorphic to racemic phenylsuccinic acid (6) may possibly be explained in a similar manner.

In the cases where X-ray investigations were performed, the method proved to be successful, since not only the racemates and the quasi-racemates were detected, but also the molecular compound between hydratropamide and α-phenylbutyramide with the same direction of rotation (5, 10). In addition, the pseudo-racemic nature of optically inactive α,β-di(2-thienyl)propionic acid was verified (5).

The X-ray powder photographs were taken in a focusing camera of Guinier type with CuK radiation (45 kV, 25 mA), using an aluminium single crystal with double curvature as monochromator (82). Because of the high intensity and consequently low time of exposure (15–20 minutes) this monochromator is very convenient. A steric relation between two compounds required six exposures (two antipodes, two racemates and two mixtures), and could be readily performed in four hours including the time required for preparation of the two mixtures.

5. INFRARED SPECTROSCOPY.—In a stereochemical study of dicarboxylic acids Rosenberg and Schotte (83) found that in some cases the existence of quasi-racemates may be indicated by their infrared spectra. The convenience of the method justifies its application to known systems, through which it is possible to find out its limitations.

A mixture of equimolar amounts of α,β-diphenylpropionic acid and α-phenyl-β-thienylpropionic acid with the same mode of rotation has an infrared spectrum which is clearly the sum of those of the components. The mixture of the components with opposite mode of rotation has considerably fewer peaks than should be expected

Table 2. Infrared absorption bands of (+)-hydratropamide and (−)-α-phenylbutyramide.

b = broad; vs = very strong; s = strong; m = medium; w = weak; sh = shoulder.

(+)-Hydratropamide			(−)-α-Phenylbutyramide		
Wave-length in μ	Wave-number in cm^{-1}	Character of the band	Wave-length in μ	Wave-number in cm^{-1}	Character of the band
3.03	3300	s	2.98	3360	s
3.17	3150	s	3.18	3140	s
3.35	2990	m	3.38	2960	m
5.13	1950	w	4.30	2325	w
5.31	1885	w	5.12	1955	w
6.02	1660	vs	5.32	1880	w
6.67	1500	s	6.03	1660	vs
6.83	1465	s	6.22	1610	m
6.88	1455	s	6.28	1590	w
7.11	1405	s	6.67	1500	w
7.28	1375	m	6.86	1460	m
7.69	1300	w	7.12	1405	m
7.82	1280	m	7.70	1300	w
7.92	1265	m sh	8.05	1240	w
8.74	1145	m	8.45	1185	w
8.99	1110	m	8.67	1155	w
9.05	1105	m	8.88	1125	w
9.4	1060	m	9.02	1110	w sh
9.72	1030	m	9.05	1105	w
9.96	1004	w	9.34	1070	w
10.06	994.0	m	9.72	1030	w
11.0	909	w	9.99	1001	w
11.7	855	w sh	10.35	966.2	w b
11.85	843.9	m b	11.08	902.5	w
12.2	820	m b	11.31	884.2	w
13.22	756.4	s	11.80	847.5	w
13.50	740.7	s	12.35	809.7	w b
13.75	727.3	m sh	12.97	771.0	w b
14.41	694.0	vs	13.25	754.7	w b
			13.92	718.4	m b
			14.35	696.9	s b

evidently indicating the quasi-racemate shown in Figure 4 of Ref. 7. On the other hand, the enantiomeric α-phenylbutyramides give mixtures with (−)-α-phenyloenanthamide having very similar spectrograms, which are probably the sum of those of the components. However, the thermal and the X-ray methods indicate a quasi-racemate between the amides with opposite mode of rotation (10, Fig. 15). The racemic amides of hydratropic and α-phenylbutyric acids show some interesting features. The racemic hydratropamide appears in the melting-point diagram as a low maximum and shows together with the antipodes far-reaching mutual solubility in the solid phase (10, Fig. 1). This mutual solubility seems to indicate a certain similarity in structure between the racemate and the antipodes (cf. 65), and one should perhaps expect small differences between the infrared spectra. The racemic phenylbutyramide appears in the diagram (10, Fig. 2) as a well-developed maximum and shows little

if any solubility in the antipode, whereas the antipode is a little more soluble in the racemate. Therefore, the differences between the racemate and the antipode seem to be greater in this case than in the former and the spectra should therefore exhibit greater differences. However, the spectra in the first case are very different, whereas the spectra in the second are almost identical.

In Figures 4 through 7 are given the infrared spectra of the optically active hydratropamide and α-phenylbutyramide and of the two molecular compounds derived from these amides (10). The differences between the molecular compound, derived from the amides with opposite rotation, and the components are evident and especially the occurrence of three bands in the N–H stretching region around 3 microns is significant. In the earlier paper dealing with these amides (10), it was suggested that the molecular compound from the amides with the same mode of rotation showed a spectrum which seemed to be the sum of those of the components. A thorough inspection of the spectra reveals, however, that some differences exist in the region between 10 and 14 microns. In particular the absence of the strong peak at 13.5 microns, derived from hydratropamide, seems difficult to explain if the preparation is a mixture of the components.

The results confirm that it is possible to detect quasi-racemates by means of infrared spectral methods which, however, seem to be less general than the thermal and X-ray methods. This may possibly be explained by the fact that the differences measured arise as secondary effects, caused by lattice disturbances of the interatomic forces.

A Perkin Elmer model 21 spectrophotometer, equipped with a sodium chloride prism, was used for the infrared absorption measurements. The samples of the amides were examined as solid pressed potassium bromide plates, according to the method described by Schiedt and Reinwein (84).

6. Polymorphism.—Refined methods of detection have revealed that a large number of organic compounds may exist in several crystalline modifications. This is also true among the compounds dealt with in this paper. It must be pointed out, however, that a search for polymorphic modifications is beyond the scope of this investigation. Therefore, the observations made are merely to be considered as results obtained along with the steric investigations, and must not be regarded as complete. Nevertheless, the study of polymorphic modifications has in some cases given valuable steric information.

As was mentioned earlier, the quasi-racemate between the hydratropamide and the α-phenylbutyramide with opposite mode of rotation is isomorphic to a less stable modification of racemic α-phenylbutyramide (Fig. 2). As this case is important from a theoretical stand-point, it seems justified to discuss it more thoroughly. The lower-melting modification of the racemate is rather unstable, and was obtained only by seeding with the quasi-racemate. A small amount of the latter was melted in under a cover glass at *A* (Fig. 8) and afterwards the racemate was introduced in the usual way (80). After cooling, the crystallized sample showed an unbroken phase between *A* and *D*. On heating, a transition front began to grow from *D* towards *B*. When the temperature was raised to 79° the sample began to melt at *B*, where the transition front was also reached. The melted region broadened to *C*, when the whole region between *C* and *E* melted at 84°. It follows then that the region between *C* and *D* was originally pure low-melting α-phenylbutyramide. The sample was rapidly cooled and after crystallisation the cold preparation was laid on the microscope, preheated

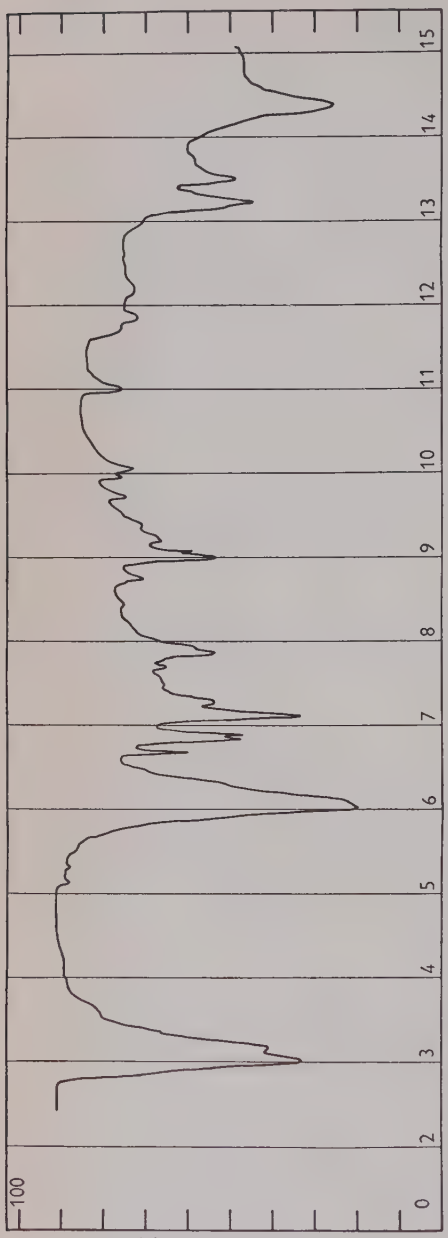


Fig. 4. IR absorption curve of (+)-hydratropamide. KBr phase.

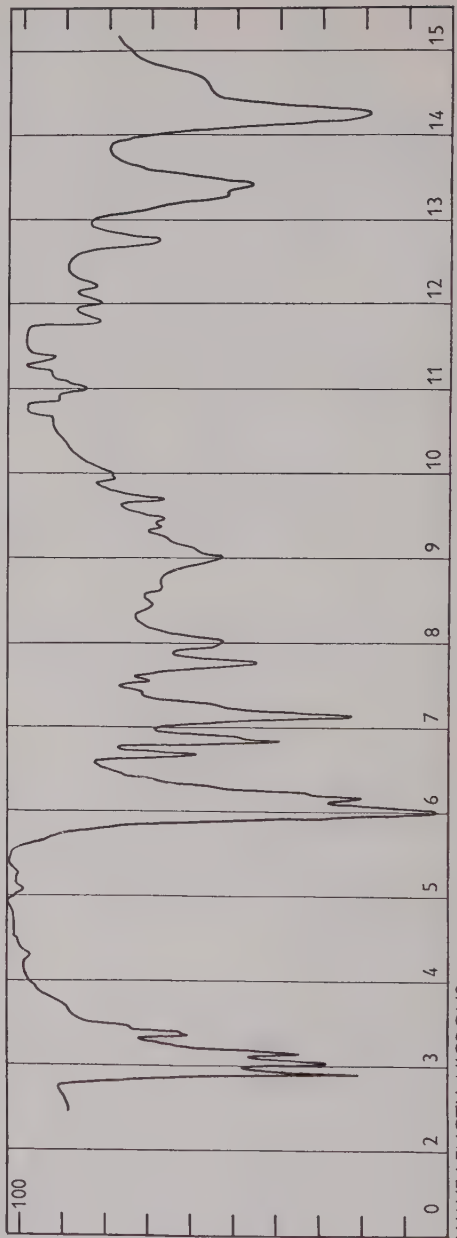


Fig. 5. IR absorption curve of the molecular compound (quasi-racemate), consisting of equimolar parts of (+)-hydratropamide and (−)-α-phenylbutyramide. KBr phase.

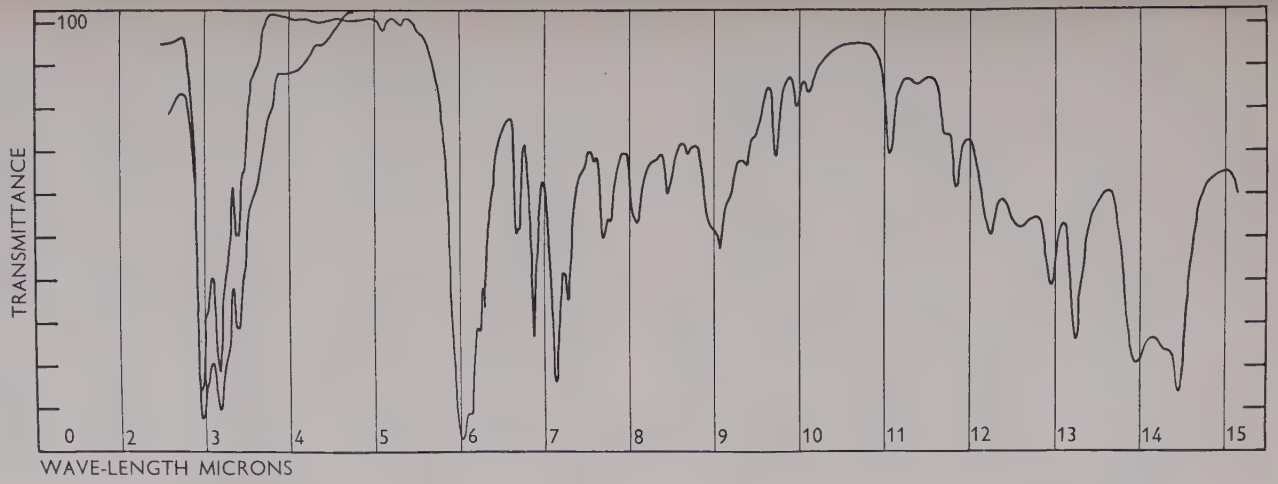


Fig. 6. IR absorption curve of the molecular compound, consisting of equimolar parts of (−)-hydratropamide and (−)-α-phenylbutyramide. KBr phase.

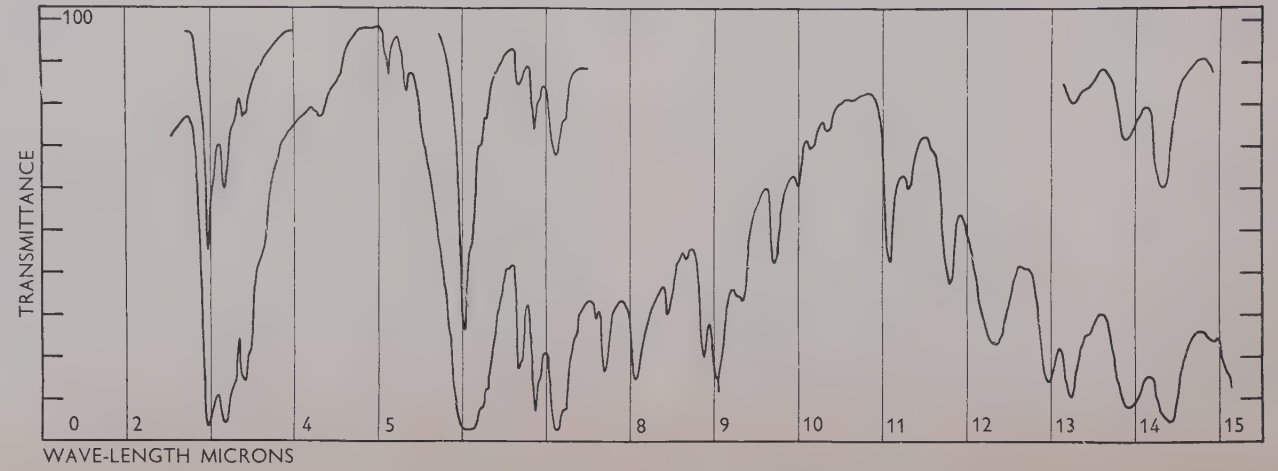


Fig. 7. IR absorption curve of (−)-α-phenylbutyramide. KBr phase.

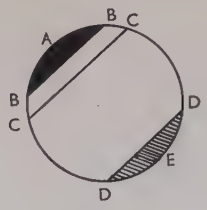


Fig. 8.

to 77–78°. This time the unstable modification between *C* and *D* melted at 80° between rapidly growing crystals of the stable modification.

The lower branch on the left-hand side of the diagram in Figure 2 was obtained only by seeding from point to point from the right-hand side. This may explain why the third modification of the quasi-racemate, constituting the end point of this lower branch, was not obtained earlier (10).

In a previous paper the melting-point diagram of (+)- and (−)-α-phenyl-β-(2-thienyl)propionic acid was reported (4, Fig. 2). A reinvestigation of the racemic acid showed that it could also exist in a second modification, melting at 66.5°. Therefore, the diagram mentioned should be completed with a lower branch between 40 % and 60 % of the (+)-acid, having the maximum at 66.5° and the end points at 65°.

Optical methods

1. THE OPTICAL DISPLACEMENT RULE.—As was emphasized above, the groups around the asymmetric carbon atom contribute to the optical activity of the compound in two different ways: by the anisotropy of their absorption bands and by their vicinal action on the other three groups (22). The vicinal rule of Kuhn (85) says that a substitution in one of the groups mainly affects the anisotropy of the absorption bands of that group, whereas the vicinal action of the group is less affected. The theoretical explanation of the optical displacement rule, formulated by Freudenberg (86), is founded on the vicinal rule. If two similarly constituted compounds with the same configuration undergo similar chemical changes, a shift of the optical activities in the same direction occurs. The reason for this is that the chemical change effects only the contribution from the attacked group and this contribution is about the same in the two compounds. The conditions for the applicability of the displacement rule are determined by the vicinal rule and may be expressed, for example, as follows: (1) the contribution to the optical activity of the groups, which are different in the compounds to be sterically related, must not be very different; (2) the contribution from the attacked groups must be sufficiently great so that a significant shift of the optical activity occurs. The second condition led Freudenberg (87) to the conclusion that a comparison between substituted phenylacetic acids should be very carefully performed, since the optical activity of these compounds are mainly determined by the phenyl group (16).

The α-phenyl fatty acids (V–IX) have been related by the displacement rule applied to the acids, amides and anilides (9, 10). The values are collected in Tables 3 and 4. The optical activities were measured in five different solvents, rendering it less probable that the differences arise as a specific effect of a special solvent. It is evident from the tables that, in fact, the differences between the optical activities of the

acids, amides, and anilides are with a few exceptions significant, and the application of the method is then justified. The reason for this may be that the contributions from the amide and anilide groups are great enough to be clearly reflected in the optical activity of the molecule. Especially the pervading high rotations of the anilides make this assumption reliable. The first-mentioned condition, concerning the differences between the compounds to be compared sterically, is also fulfilled, since *n*-alkyl groups usually have very similar properties. (Compare, however, the amines VIIa, VIIIa and IXa discussed above).

2. Comparison of optical activities in different solvents.—The influence of the solvent on the optical activity of a solute is a very complicated matter (88). Nevertheless, a comparison of the optical activities of two similarly constituted compounds in a series of solvents may give information about the steric relation between them (89, 90). If the optical rotations of the compounds are shifted in the same direction when progressing through the series of solvents, the compounds have the same configuration. If not, no conclusion about the steric relation can be drawn.

The complicated nature of the solvent action makes it obvious that the structural differences between the compounds must be small. It is difficult also to predict how large the differences may be before the method becomes invalid. It seems less surprising, however, that a comparison between, for example, the tetrahydronaphtoic acids and α-phenylvaleric acid fails (91). On the other hand, the reason why a comparison between α-phenoxybutyric acid and α-(1-naphtoxy)butyric acid gives a posi-

Table 3. Optical activities ($[M]_D^{25}$) of *dextro*-rotatory derivatives[1] (8, 10, 42).

Compounds compared	Ethanol			Acetone			Acetic acid		
	amide	acid	anilide	amide	acid	anilide	amide	acid	anilide
Hydratropic acid (IX) . .	69.3°	119°	271°	70.1°	143°	216°	21.2°	131°	216°
Phenylbutyric acid (VIII)	92.3°	129°	253°	92.3°	168°	197°	43.9°	138°	219°
Phenylvaleric acid (VII) .	88.5°	114°	237°	88.2°	157°	184°	48.9°	128°	212°
Phenylcaproic acid (VI) .	80.1°	119°	222°	86.4°	158°	198°	55.8°	138°	210°
Phenyloenanthic acid (V)	95.6°	122°	229°	97.4°	160°	192°	80.3°	134°	221°

Table 4. Optical activities ($[M]_D^{25}$) of *dextro*-rotatory derivatives[1] (8, 10, 42).

Compounds compared	Ether			Benzene		
	acid	amide	anilide	acid	amide	anilide
Hydratropic acid (IX)	—	117°	344°	140°	137°	287°
Phenylbutyric acid (VIII) . . .	133°	163°	378°	157°	187°	327°
Phenylvaleric acid (VII)	118°	163°	363°	136°	172°	338°
Phenylcaproic acid (VI)	125°	156°	356°	144°	161°	330°
Phenyloenanthic acid (V)	124°	190°	361°	148°	191°	348°

[1] For convenience, the rotations have been assigned the *dextro*-compounds even if they are measured on their antipodes.

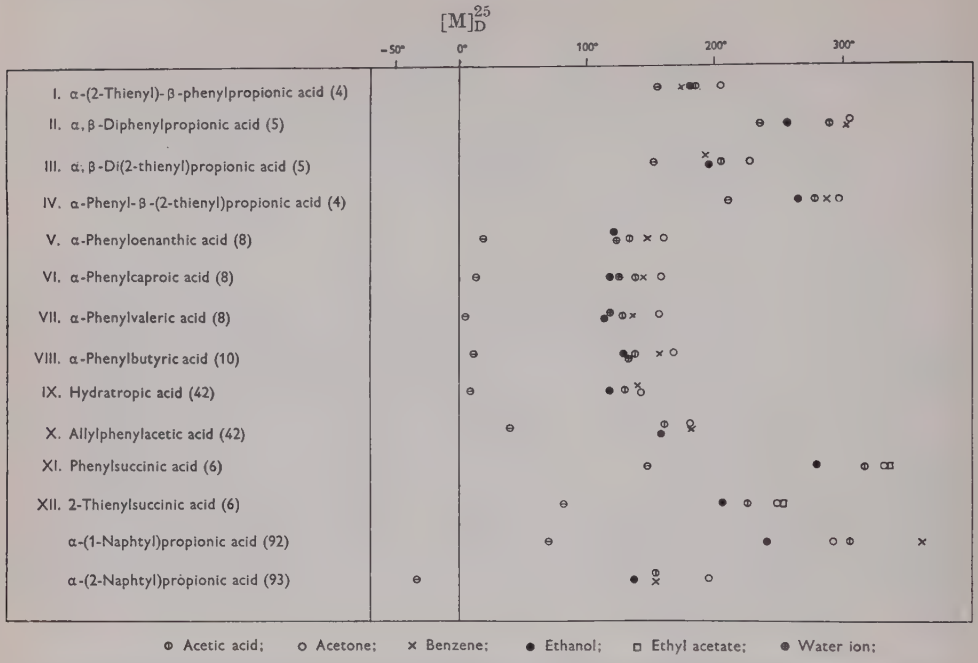


Fig. 9. Optical rotation ($[M]_D^{25}$) in different solvents of sterically related α-aryl carboxylic acids.

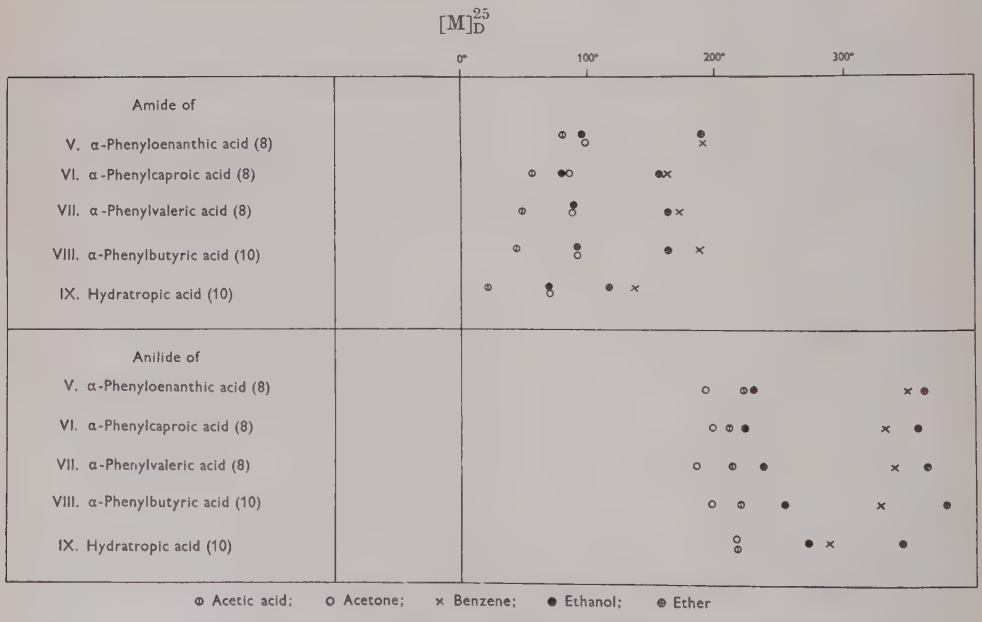


Fig. 10. Optical rotation ($[M]_D^{25}$) in different solvents of amides and anilides of sterically related α-phenyl fatty acids.

tive result but not a comparison between α-phenoxybutyric acid and α-(2-naphtoxy)butyric acid seems more difficult to explain (90). However, the special properties of the α-aryl carboxylic acids investigated allow some generalisations to be made.

In the paragraph dealing with the optical activities it was emphasized that the optical rotation of the α-aryl carboxylic acids mainly depends on the absorption bands of the α-aryl group, whereas the contribution from chromophores located at a distance from the asymmetric center is less important. An interaction of the solvent with the chromophores (a vicinal action from the solvent) should then be similar for compounds containing the same aryl group at the center. But the optical activity depends on the vicinal action of the remaining groups also. It is reasonable to suppose that a solvent action on these groups is mainly concerned with a strongly polar group. Therefore, compounds containing both a phenyl and a carboxyl group but no other chromophoric or polar group directly attached to the asymmetric center, would probably show a similar dependence on the solvent. The behaviour of a series of compounds is shown diagramatically in Figs. 9 and 10. All of the phenyl carboxylic acids have hydrogen as a common third group. The fourth group is, however, different, being arylmethyl (II, IV), alkyl (V–IX), allyl (X) and carboxymethyl (XI). In spite of these important structural differences, all of the acids show *exactly the same sequence of solvents*. It is rather probable that all α-phenyl carboxylic acids, which fulfil the requirements outlined above, may be sterically related by means of this method.

Comparison of the compounds with different α-aryl groups affords some interesting observations also. The α-(2-thienyl)propionic acids (I, III) differ from the phenyl analogs only in the position of the benzene dot (Fig. 9). It is evident that the significant parallellism between the behaviour of the related acids is a strong indication of the D-configuration of α,β-di(2-thienyl)propionic acid (III), which could not be related by other means. The arylsuccinic acids show the same sequence of solvents, but these acids were not measured in benzene. The values of α-(1-naphtyl)- and α-(2-napthyl)-propionic acids show that these compounds may also be included in the system.

The far-reaching similarities of the compounds with different α-aryl groups are in sharp contrast to the differences which occur, when the carboxyl group is replaced by amide or anilide groups (Fig. 10). However, the series of amides as well as the series of anilides each show a particular solvent sequence, clearly indicating the steric relation. This seems to indicate that the solvent acts predominantly on the polar carboxyl, amide and anilide groups.

Experimental

Catalytic reduction of α-phenyl fatty amides

(+)-*Hydratropamide:* 0.6 g of the (+)-amide was dissolved in dry ether and made up to 50 ml. The optical activity was measured in a 2 dm tube. $2\,\alpha_D^{23} = +1.9°$. The solution was added dropwise to a slurry of 0.2 g of lithium aluminium hydride in dry ether. When all the solution was added, the mixture was refluxed for half an hour and then 0.2 ml of water and 2 ml of 5 *N* sodium hydroxide were added successively. The pasty precipitate formed was extracted repeatedly with ether, and the ether fractions combined and dried. The optical activity was measured as before: $2\,\alpha_D^{23} = +0.4°$. The ether solution was treated with an excess of dry hydrochloric acid in

methanol and the mixture evaporated to dryness. The residue was extracted repeatedly with ether and finally recrystallized from a mixture of methanol and ether. The hydrochloride of α-phenylpropylamine was obtained as colourless needles, melting at 140–142°.

0.090 g of the chloride was dissolved in *ethanol* and made up to 10.0 ml: $2\,\alpha_D^{25} = -0.33°$, $[\alpha]_D^{25} = -18°$. 0.110 g in *water*: $2\,\alpha_D^{25} = -0.47°$, $[\alpha]_D^{25} = -21°$.

The hydrochloride was dissolved in water and the amine was liberated with 33 % sodium hydroxide and extracted with ether. The ether was removed and the residue evacuated at room temperature. 0.121 g of the remaining amine was dissolved in *ether*: $2\,\alpha_D^{25} = -0.39°$, $[\alpha]_D^{25} = -16°$. 0.136 g in *ethanol*: $2\,\alpha_D^{25} = -0.50°$, $[\alpha]_D^{25} = -18°$. 0.102 g in *75 % ethanol*: $2\,\alpha_D^{25} = -0.43°$, $[\alpha]_D^{25} = -21°$. Optical activity of the amine in the *homogenous state*: $0.5\,\alpha_D^{25} = -4.2°$, $[\alpha]_D^{25} = -8.4°$.

The ether washings, made before recrystallization of the hydrochloride, were combined and evaporated to 10 ml. The optical activity was measured: $2\,\alpha_D^{25} = +1.4°$.

(+)-α-*Phenylbutyramide:* 0.5 g of the (+)-amide was dissolved in 10 ml of dry ether: $2\,\alpha_D^{23} = +9.10°$. The hydrogenation was performed as described above. The ether washings, containing the amine, were combined and dried and the optical activity of the solution, which amounted to 25 ml, was measured: $2\,\alpha_D^{25} = +0.80°$. The amine was converted to hydrochloride as described above. The salt was obtained as colourless crystals, melting at 165–166°.

0.1033 g of the hydrochloride was dissolved in *ethanol* and made up to 10.0 ml and the activity measured: $2\,\alpha_D^{25} = -0.12°$, $[\alpha]_D^{25} = -5.8°$. 0.118 g in *water*: $2\,\alpha_D^{25} = -0.15°$, $[\alpha]_D^{25} = -6.4°$.

The amine was liberated and isolated as described above. 0.121 g in *ether*: $2\,\alpha_D^{25} = +0.25°$, $[\alpha]_D^{25} = +10°$. 0.119 g in *ethanol*: $2\,\alpha_D^{25} = -0.24°$, $[\alpha]_D^{25} = -10°$. 0.090 g in *75 % ethanol*: $2\,\alpha_D^{25} = -0.13°$, $[\alpha]_D^{25} = -7.2°$. Optical activity in the *homogenous state*: $0.5\,\alpha_D^{25} = +2.3°$, $[\alpha]_D^{25} = +4.6°$.

(+)-α-*Phenylvaleramide:* 1.2 g of the amide was dissolved in 50 ml of dry ether and the optical activity measured. $2\,\alpha_D^{25} = +4°$. The amide was hydrogenated as described above. The ether solution of the amine, which occupied 50 ml, was measured. $2\,\alpha_D^{25} = +0.63°$. The amine was converted to the hydrochloride, which was obtained as colourless needles melting at 208–210°.

0.110 g of the hydrochloride was dissolved in *water* and made up to 10.0 ml: $2\,\alpha_D^{25} = -0.15°$, $[\alpha]_D^{25} = -6.8°$.

The amine was liberated and isolated as described for the lower homologues. 0.137 g in *ether*: $2\,\alpha_D^{25} = -0.19°$, $[\alpha]_D^{25} = -6.9°$. 0.261 g in *ethanol*: $2\,\alpha_D^{25} = -0.46°$, $[\alpha]_D^{25} = -8.8°$. 0.196 g in *75 % ethanol*: $2\,\alpha_D^{25} = -0.27°$, $[\alpha]_D^{25} = -6.9°$. Optical activity in the *homogenous state*: $0.5\,\alpha_D^{25} = -2°$, $[\alpha]_D^{25} = -4°$.

To prevent loss of the material, the amines were recovered from the measured solutions by evaporation of the solvent. The amines were used without further purification for the measurements in other solvents. Therefore, the values obtained must not be considered as very accurate.

Melting-point diagrams

Melting-point preparations: Stock solutions of the two molecular compounds, obtained from the amides of hydratropic acid and α-phenylbutyric acid, and of racemic α-phenylbutyramide were prepared in acetone. ("AnalaR" standards for laboratory chemicals). The desired mixtures were obtained by mixing appropriate

Table 5. Molecular compound of amides with opposite direction of rotation and racemic phenylbutyramide.

Mole % phenyl-butyramide	Melting point °C		
0	76	91.5	93
10			87 –89
20			84 –86.5
27	68		82.5–85
40	63.5		80.5–82.5
50	69.5		79.5–81.5
60	74		79 –80.5
70	77		79 –80
80	79.5		79 –80
85	80		–81
90	80		–82.5
100	80		–84

Table 6. Molecular compound of amides with the same direction of rotation and racemic phenylbutyramide.

Mole % phenyl-butyramide	Melting point °C	
0	66	70.5
10	64	68
20		65.5
30	60	66.5
40	57.5	70.5
50	67	73
60	71	77
70	75	78.5
80		61–80
90		61–82
100	80	84

amounts of the stock solutions, the solvent was removed and the residue carefully powdered and dried in a desiccator. The melting points were observed in a Kofler hot-stage microscope. The lower melting points, as shown by the dotted curves in Figs. 2 and 3, were obtained after premelting and rapid cooling of the samples under a cover-glass. Seeding of the samples was performed by scratching with a spatula dipped in the appropriate seeding material.

Summary

By means of experimental results reported in this and previous papers, a comparison between α-substituted phenyl and 2-thienyl carboxylic acids is made (Fig. 1, p. 299). The configurations of the compounds were related to D-glyceraldehyde.

The optical activities of the phenyl acids were throughout higher than those of the corresponding 2-thienyl compounds. It was assumed that the optical activity of the substituted 2-thienylacetic acids, in analogy with the corresponding phenyl derivatives, is mainly determined by the anisotropic bands of the aromatic group. The values of the optical activities indicate that the influence of chromophoric groups, separated from the asymmetric carbon atom by a methylene group, is less important. An indication of the optical purity of (−)-α,β-di(2-thienyl)propionic acid was emphasized.

The chemical and physical methods, used in the determination of steric relations, were briefly reviewed. In connection with the quasi-racemate method the conditions for racemate and quasi-racemate formation were discussed. Considerable differences in the ability for racemate formation were found between analogously constituted phenyl and 2-thienyl compounds.

The fact that (−)-α-phenylbutyramide gives molecular compounds with both (+)- and (−)-hydratropamide was discussed and the application of the quasi-racemate method in such cases demonstrated (Figs. 2 and 3, p. 310).

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